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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,481	02/27/2002	Hiroaki Takayama	TAKAYAMA10	3430

1444 7590 04/09/2003

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EXAMINER
QAZI, SABIHA NAIM

ART UNIT	PAPER NUMBER
1616	10

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,481	TAKAYAMA ET AL.	
	Examiner	Art Unit	
	Sabiha Naim Qazi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1, Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 & 5.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Invention: The instant invention is drawn to 2-substituted vitamin D_3 derivative, their composition and method of use.

Acknowledgement is made of the response, declaration and request for reconsideration filed on 1/10/03 and /12/03. Claims 1-15 are pending and rejected. No claim is allowed. Preliminary amendments are entered.

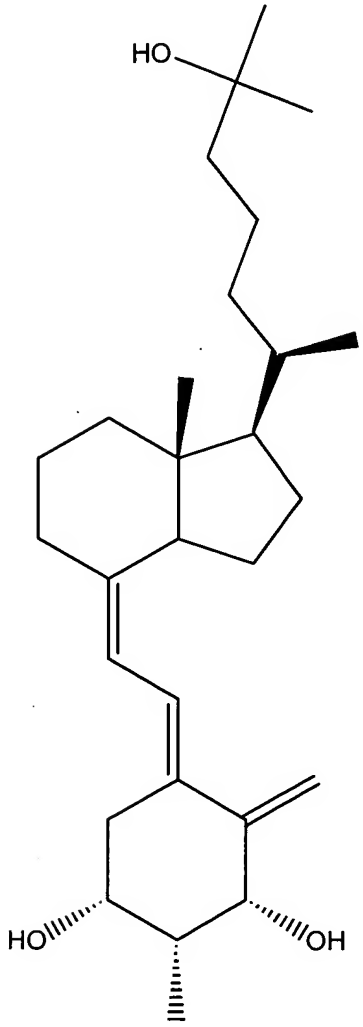
Rejection over Miyamoto, Ono is withdrawn because of the declaration filed by applicants. Other rejections are maintained because arguments are not found persuasive.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

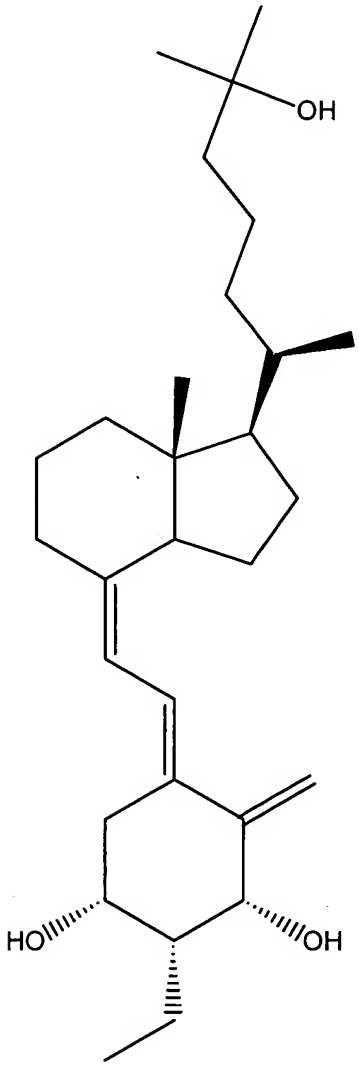
A person shall be entitled to a patent unless –

1. Claims 1-15 rejected under 35 U.S.C. 102(b) as being anticipated by Konno et al. (Bioorganic & and Medicinal Chemistry Letters 8 (1998) 151-156 and Fujishima et al. (Bioorganic & and Medicinal Chemistry Letters, (1998), 2145-2148). In Konno reference see compound Table I and lines Its Para on page 154. See compound 4 on page 155. Note that compound having 2-alpha substitutions is better than the beta position. See compound 3 on page 2145 and compound 4 on page 2146 in Fujishima et al.



2alpha-methyl-1alpha,25-dihydroxyvitamin D3

2. Claims 1-15 rejected under 35 U.S.C. 102(b) as being anticipated by Posner et al. (WO 96/01811). See compound 3 on page 4, 3rd compound on page 36, compound of claims 3 and 4.



2alpha-ethyl-1alpha,25-dihydroxyvitamin D3

1. Claim 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Konno et al. (Bioorganic & and Medicinal Chemistry Letters 8 (1998) 151-156) and Fujishima et al. (Bioorganic & and Medicinal Chemistry Letters, (1998), 2145-2148). See the entire documents especially In Konno reference see compound Table I and lines Ist para on page 154. See compound 4 on page 155. See compound 3 on page 2145 and compound 4 on page 2146 in Fujishima et al. These references

disclose that 20-epi-alpha-alpha-beta analogue exhibited 12-fold higher affinity than 1-alpha, 25-dihydroxyvitamin D3, whereas alpha-beta-beta has comparable activity to 1-alpha, 25-dihydroxyvitamin D3. See second para and Table 1on page 2147 of Fujishima reference.

Presently claimed invention differ from the reference in that they are of different generic scope. It had been held by Courts that the indiscriminate selection of "some" from among "many" is considered prima facie obvious. In re Lemin, 141 USPQ 814 (1964); National Distillers and Chem. Corp. V. Brenner, 156 USPQ 163.

The instant claimed compounds would have been obvious because one skilled in the art would have been motivated to prepare compounds embraced by the genus of the above cited references with the expectation of obtaining additional beneficial compounds useful as antitumor agents, an immunomodulator etc.

One having ordinary skill in the art would be motivated to prepare additional derivatives of vitamin D_3 because prior art teaches 2-substituted vitamin D derivatives for various uses. It would have been obvious who is even familiar with the art at the time of invention to prepare the compounds and compositions for various uses as instantly claimed.

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

What is the meaning of "therapeutic agent for a disease associated with abnormal calcium metabolism" in claims 1-15.

What is intended by the term "derivatives" in claims? This term must be deleted.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The nature of the invention

Presently claimed invention is drawn to 2-alpha -substituted vitamin D compound and their method of use.

The predictability or unpredictability of the art: There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Therefore predicting the method of treating or inhibiting various disease states by compounds of broad genus is impossible. AS in claim 1 R1 represents a saturated aliphatic C1-15 hydrocarbon group optionally substituted with 1 to 3 hydroxy or protected hydroxy groups, which is considered broad. The data of binding activity of compounds 31-35 shows that in all examples R1 is same the change was only at 2-position substituent. In the vitamin D area it is impossible to predict the activity of the compounds for a broad genus and for the treatment of various disease.

As an example Examiner would like to refer Applicant's own declaration for a comparative data showing that alpha substituted compound has better than beta compound. These beta compounds are disclosed in Miyamoto reference. Since even a minor change in being a stereoisomer can change the activity, therefore claiming all the compounds and their activity would be impossible.

The amount of direction or guidance presented

A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See *In re Riat* et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result".

See *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

The presence or absence of working examples

There no examples or test data in vivo or in vitro to support all the methods as presently claimed. The data on page 51 of the specification shows binding

property of compounds 31-35. No other data or any other test in vitro or in vivo is disclosed.

The quantity of experimentation necessary

Since different aspects of biological activity cannot be predicted but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue experimentation study.

Since the nature of the method is so unpredictable, and since the claims are drawn to a broad range of pharmaceuticals for treatment of such a broad range of disease states, and since there is a lack of guidance present in the specification, the skilled artisan would have to undertake undue experimentation to practice the claimed invention commensurate with the scope of the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 3 claims of co pending Application No. 09/214,155 and claims 1-3, 5-8 and 10-13 of 09/959,541 respectively. Although the conflicting claims are not identical, they are not patent ably distinct from each other because 2-position of vitamin D represents lower alkyl group and it is claimed in 10/069,481. In claim 1 of 09/214,155 a methyl group at alpha and beta position is claimed at 2- position, which is considered obvious because a methyl group is included in lower alkyl group. In 10/069,481 vitamin D3 is 2-substituted alkyl. In all the above copending applications and presently claimed invention 2-substituted vitamin D3 compounds are claimed which are considered obvious over the other.

Applicants must disclose all the copending and any patent related to this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabina Maim Quiz whose telephone number is 703-305-3910. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose Dees can be reached on 703-308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

S. Qazi

SABIHA QAZI, PH.D
PRIMARY EXAMINER